Collaborative Guidelines On The Diagnosis Of Porphyria And Related Conditions

Prepared By

The Washington State Department of Labor and Industries
And
The Washington State Medical Association's
Committee On Industrial Insurance And Rehabilitation

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Purpose and Development of these Guidelines

The purpose of these guidelines is to provide information for treating physicians and independent medical examiners to use in evaluating patients with possible exposure-related porphyria, and to provide a foundation for developing Department medical policy.

The focus of these guidelines is on the phase of the medical evaluation where a decision must be made whether to proceed with an extensive work-up to reach a definitive diagnosis, or to conclude that results of a preliminary evaluation make a diagnosis of porphyria unlikely (see Section III). It is beyond the scope of these guidelines to provide detailed algorithms for reaching a conclusive diagnosis.

These guidelines were developed with the input and approval of numerous nationally and internationally recognized experts on porphyria. Input was also incorporated from many other individuals, including physicians representing a wide variety of specialties and non-physicians with an interest in this topic.

The scientific basis for these guidelines, along with additional information about their development, can be found in a review document on porphyria prepared by the Office of the Medical Director of the Washington State Department of Labor and Industries. These guidelines may be revised as new scientific information becomes available.

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Date Introduced: October 1995

General Information

Porphyrias are metabolic disorders in which the clinical manifestations are attributable to decreased activity of a specific enzyme(s) in the heme synthesis pathway, associated with characteristic patterns of overproduction of specific heme precursors and resultant accumulation in certain tissues. Each enzyme deficiency results in a predictable accumulation of the preceding heme precursor(s), and overall production of heme is generally preserved. Porphyrias, when clinically active, and in some cases even when latent or in clinical remission, are characterized by high levels of heme precursors in blood, urine, and/or stool. Most types of porphyria are inherited conditions; however, one type of porphyria, porphyria cutanea tarda, is known to occur in acquired or inherited manner.

Many of the tests used to diagnose the porphyrias are nonspecific and are abnormal in many circumstances other than the porphyrias. Porphyrinuria, i.e., increased urine porphyrins, can be caused by porphyrias, by a number of other medical conditions, and by a variety of exogenous factors such as alcohol and certain drugs and chemicals that disturb heme synthesis or stress heme-dependent metabolism. The term "secondary porphyrinuria" is commonly used in reference to the porphyrinuria occurring with conditions and factors lacking a primary enzyme defect in heme synthesis. It usually involves mild or moderate coproporphyrinuria, with no or little excess uroporphyrin in urine, and is also often called "coproporphyrinuria" or "secondary coproporphyrinuria."

In individuals who are genetically predisposed to developing an acute or cutaneous porphyria, manifestations of porphyria can be *triggered* by a variety of exogenous factors including alcohol, certain therapeutic drugs and chemicals, infections, dietary factors and sun exposure, as well as by certain medical conditions and endogenous factors such as menstruation and administered steroid hormones. Exogenous factors can also *cause* changes in the heme synthesis pathway, even in the absence of genetic predisposition; in some cases, these acquired changes have been reported to cause porphyria cutanea tarda.

Lead absorption, both acute and chronic, is well documented to affect heme synthesis. Lead causes accumulation of protoporphyrin in erythrocytes and large increases of ALA and coproporphyrin in urine. Lead inhibits ALA dehydratase, and also appears to interfere with the function of two other heme synthesis enzymes. Lead intoxication is generally classified as a secondary porphyrinuria rather than as an acquired porphyria, although it does have clinical and biochemical similarities with acute porphyrias.

A number of chemicals, primarily halogenated hydrocarbons and metals, are known to be "porphyrogenic" (i.e., capable of inducing changes in heme synthesis, with subsequent overproduction and excessive excretion of heme precursors) in experimental animals, generally with doses much greater than the range of human experience. In humans, with the noteworthy exceptions of porphyria caused by hexachlorobenzene and the "porphyrinuria" caused by lead, reports of porphyria or porphyrinuria attributable to chemical exposures have been infrequent. It must be acknowledged, however, that there has been only limited systematic study of the subject in humans. The reported

findings have generally been linked to chronic industrial exposures, industrial accidents, or environmental exposures that were much higher than normally encountered.

Diagnosis

The most important first step toward diagnosing or ruling out porphyria in a symptomatic patient is for the physician to maintain a high index of suspicion for a possible diagnosis of porphyria, whether symptoms are "classic" for a porphyria or are vague or unexplained. The conclusive diagnosis of a porphyria should be based on a systematic approach incorporating medical history, physical examination, and biochemical data, including genetic evaluation if necessary. Certain symptom patterns, physical findings, and elements of the exposure history may raise the degree of suspicion for porphyria; however, the lack of supporting information from these sources cannot exclude a diagnosis of porphyria. Therefore, the systematic approach to evaluating a symptomatic patient with suspected porphyria should begin with laboratory evaluation.

In a person with symptoms from a porphyria, the level of the most excessively excreted heme precursor is typically at least several-fold greater than the upper limit of values found in normal individuals.

A. Minimum ("Threshold") Criteria

Physicians must sometimes decide whether an extensive work-up for porphyria is indicated. In order to assist clinicians in this decision, the following threshold criteria are recommended:

In a patient who is currently or recently symptomatic and who is suspected to have a porphyria, it is not probable that the patient's symptoms are attributable to a porphyria of any type unless a measurement on at least one of the following tests is greater than twice the upper limit of normal:

- **urine porphobilinogen (PBG)**
- **urine uroporphyrin**
- **urine coproporphyrin**
- **fecal coproporphyrin**
- **blood total porphyrins**

B. Caveats

1. **Reference range:** Because a reference range may be unique to the assay method and the individual laboratory performing the test, test results should be interpreted relative to the laboratory-specific reference range and/or, if sufficient general clinical experience exists, against accepted absolute reference standards.

2. **Blood Lead Level:** A blood lead level should be checked to determine the possibility of lead intoxication if lead exposure is suspected, if excretion of

coproporphyrin or ALA is increased, or if blood porphyrins (e.g., blood zinc protoporphyrin [ZPP]) are increased.

3. **Repeat testing and factors affecting test results:** Laboratory test results, in general, can be compromised by a variety of factors including specimen integrity, analytical quality, limitations of analytical methods, and the applicability and specificity of reference ranges or "control" data. Issues of specimen integrity may be particularly relevant when specimens are collected and processed at one site, and then transported to a geographically distant reference laboratory.

   Because of these risks, an abnormal test result generally should be confirmed by analysis of a second specimen before the test result is used to finalize a diagnostic conclusion. The need to repeat a test, of course, must be tempered by the degree of support for a diagnosis from other clinical and laboratory data, and by the feasibility of repeating the test (i.e., the appropriate clinical circumstances should still be present).

4. **Enzyme measurements:** If a person is currently or recently symptomatic and is found to have reduced activity of a specific heme synthesis enzyme, but laboratory testing does not also reveal overproduction and excessive excretion of heme precursors in a pattern and levels consistent with the porphyria specific to that enzyme, then the reduction in measured enzyme activity has no probable causative relationship to the person's symptoms.

5. **Additional testing:** Satisfaction of these "twice the upper limit of normal" criteria *does not necessarily establish* a diagnosis of porphyria. Depending on the degree and pattern of abnormalities on these tests, additional testing may be necessary to establish or exclude a diagnosis of porphyria. It is possible that an individual could have an abnormal heme precursor measurement with this degree of abnormality (i.e., twice upper normal) as a consequence of something other than porphyria (or lead intoxication). Other medical conditions can cause "secondary" porphyrinuria of this magnitude. Blood porphyrins can also be increased by this magnitude in conditions other than porphyria: for example, iron deficiency commonly produces an increase in blood zinc protoporphyrin (ZPP).

6. **Timing of specimen collection:** Conversely, failure to satisfy these "twice the upper limit of normal" criteria *does not necessarily exclude* a diagnosis of porphyria. Heme precursor measurements in the range of one to two times the upper normal value should not be interpreted as "normal," but rather as *indeterminate or non-diagnostic*. When a patient with suspected porphyria is not currently or recently symptomatic, the levels of heme precursor excretion are generally lower and can even normalize with time. If a patient's last symptoms occurred remotely in time relative to specimen collection, it may be necessary to repeat the tests during or as soon as possible after future symptoms.

7. **"Secondary porphyrinuria":** Porphyrinuria sometimes secondarily reflects the presence of a medical condition or exogenous factor that disturbs heme

synthesis or stresses heme-dependent metabolism but produces symptoms through a separate mechanism. With the noteworthy exception of lead poisoning, the porphyrin excess in "secondary porphyrinuria" has no recognized, clinically detectable consequences of its own; symptoms associated with secondary porphyrinuria (other than lead poisoning) are attributed by most experts to the condition or agent causing the porphyrinuria, or to an unrelated cause, and not to a disturbance in heme synthesis. Although the porphyrinuria itself may be benign, the associated medical condition may be far from benign.

Medical conditions that appear to have only secondary effects on the heme synthesis pathway are appropriately evaluated with attention focused on the primary condition. Similarly, when chemical exposures are suspected as the cause of a patient's symptoms or medical condition, the exposure relationship can be characterized more specifically by assessment of the exposure situation or by quantification of the suspected chemical (or its metabolite) in blood or urine, than by measurement of heme precursors.

Complex Regional Pain Syndrome (CRPS)

Formerly known as Reflex Sympathetic Dystrophy

1. INTRODUCTION

This bulletin outlines the Department of Labor and Industries' guidelines for diagnosing and treating Complex Regional Pain Syndrome (CRPS) – formerly known as Reflex Sympathetic Dystrophy (RSD). This guideline was developed through collaboration between the Washington State Medical Association (WSMA) Industrial Insurance/Rehabilitation Committee and the Office of the Medical Director of the Department of Labor and Industries. The protocol for CRPS physical therapy/occupational therapy (see Table 2) was developed in collaboration with the Washington State Physical Therapy and Occupational Therapy Associations.

2. WHAT IS COMPLEX REGIONAL PAIN SYNDROME?

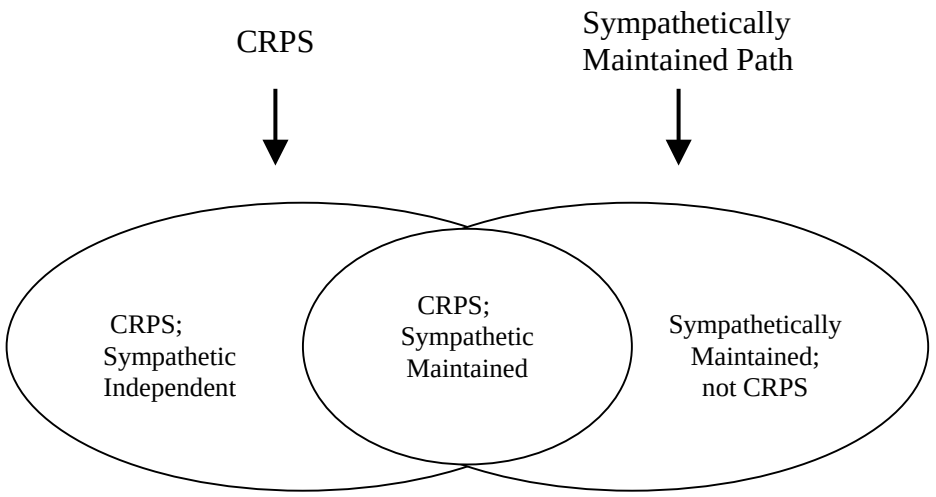
Complex Regional Pain Syndromes are painful conditions that usually affect the distal part of an upper or lower extremity and are associated with characteristic clinical phenomena as described in Table 1. There are two subtypes – CRPS Type I and CRPS Type II.

The term "Complex Regional Pain Syndrome" was introduced to replace the terms "reflex sympathetic dystrophy." CRPS Type I used to be called reflex sympathetic dystrophy. CRPS Type II used to be called causalgia. The terminology was changed because the pathophysiology of CRPS is not known with certainty. It was determined that a descriptive term such as CRPS was preferable to "reflex sympathetic dystrophy" which carries with it the assumption that the sympathetic nervous system is important in the pathophysiology of the painful condition.

The terms CRPS Type I and CRPS Type II are meant as descriptors of certain chronic pain syndromes. They do not embody any assumptions about pathophysiology. For the most part the clinical phenomena characteristics of CRPS Type I are the same as seen in CRPS Type II. The central difference between Type I and Type II is that, by definition, Type II occurs following a known peripheral nerve injury, whereas Type I occurs in the absence of any known nerve injury.

Reference: Provider Bulletin 97-05; Date Introduced: June 1997

Pain that can be abolished or greatly reduced by sympathetic blockade (for example, a stellate ganglion block) is called sympathetically maintained pain. Pain that is not affected by sympathetic blockade is called sympathetically independent pain. The pain in some CRPS patients is sympathetically maintained; in others, the pain is sympathetically independent. The relation between CRPS and sympathetically maintained pain can be seen in the following Venn diagram:



**************************PHYSICIANS PLEASE NOTE***************************

If you believe the CRPS condition is related to an *accepted occupational injury*, please provide written documentation of the relationship (on a more probable than not basis) to the original condition. Treatment for CRPS will only be authorized if the relationship to an accepted injury is established.

3. DIAGNOSTIC CODES

After treatment authorization has been obtained from the claim manager, physicians should use billing codes that are designated for reflex sympathetic dystrophy in the International Classification of Diseases (ICD-9CM) to bill. The relevant code numbers are described below:

ICD 9-CM Code	English Description
337.20	Reflex sympathetic dystrophy, unspecified
337.21	Reflex sympathetic dystrophy of the upper limb
337.22	Reflex sympathetic dystrophy of the lower limb
337.29	Reflex sympathetic dystrophy of other specified site

4. KEY ISSUES IN MAKING A DIAGNOSIS

A. CRPS is a Syndrome – See whether your patient's symptoms and signs match those described in Table 1.

B. CRPS is Uncommon - Most patients with widespread pain in an extremity do **NOT** have CRPS. **Avoid the mistake of diagnosing CRPS primarily because a patient has widespread extremity pain that does not fit an obvious anatomic pattern.** In many instances, there is no diagnostic label that adequately describes the patient's clinical findings. It is often more appropriate to describe a patient as having "regional pain of undetermined origin" than to diagnose CRPS.

C. Is CRPS a Disease? – Many clinicians believe that CRPS can best be construed as a "reaction pattern" to injury or to excessive activity restrictions (including immobilization) following injury. From this perspective, CRPS may be a complication of an injury or be iatrogenically induced but it is not an independent disease process.

D. Type I CRPS vs. Type II CRPS – In a patient with clinical findings of CRPS, the distinction between Type I and Type II CRPS depends on the physician's assessment of the nature of the injury underlying the CRPS. In many situations, the distinction is obvious – if CRPS onsets following an ankle sprain or a fracture of the hand, it is Type I CRPS. If CRPS onsets following a gunshot wound that severely injures the median nerve, it is Type II CRPS. In ambiguous situations (for example CRPS in the context of a possible lumbar radiculopathy), the physician should be conservative in diagnosing Type II CRPS. This diagnosis should be made only when there is a known nerve injury with definable loss of sensory and/or motor function.

5. TYPICAL CLINICAL FINDINGS

A diagnostic algorithm that details the following clinical findings is located in Table I at the end of this guideline.

A. History

1. Symptoms develop following injury (usually symptoms begin within 2 months post injury).
2. Onset is in a single extremity
3. Burning pain
4. Hyperalgesia or allodynia (allodynia means pain elicited by stimuli that normally are not painful, i.e., a patient reports severe pain in response to gentle stroking of the skin.)
5. Swelling
6. Asymmetry or instability of temperature or color
7. Asymmetry or instability of sweating
8. Trophic changes of skin, nails, hair

B. Findings by Examination

1. Hyperalgesia or allodynia
2. Edema (if unilateral, and other causes excluded)
3. Vasomotor changes such as asymmetry or instability of temperature/color
4. Sudomotor changes such as excess perspiration in affected extremity
5. Trophic changes such as shiny skin, hair loss, abnormal nail growth
6. Findings suggestive of impaired motor function such as:

   (a) tremor
   (b) abnormal limb positioning
   (c) diffuse weakness that cannot be explained by neuralgic loss or by dysfunction of joints, ligaments, tendons or muscles.

C. Diagnostic Test Results

A three-phase bone scan with characteristic pattern of abnormality. (NOTE – An abnormal bone scan is **not** required for the diagnosis of CRPS.)

D. Lack of Reasonable Alternative

No other anatomic, physiologic or psychological condition that would reasonably account for the patient's pain and dysfunction.

6. SYMPATHETIC BLOCKADE IN THE DIAGNOSIS OF CRPS

A. CRPS is considered a clinical syndrome, based on the criteria previously described in typical clinical findings and detailed in Table 1.

B. A patient's response to a diagnostic sympathetic block provides information about whether his/her pain is sympathetically maintained, but neither establishes nor refutes a diagnosis of CRPS. Therefore, a sympathetic block is not considered to be a definitive diagnostic test for CRPS.

C. In the patient with CRPS the purpose of a sympathetic block is to guide treatment. If a CRPS patient responds positively to a sympathetic block (indicating that his/her pain is sympathetically maintained) repeat blocks might be useful in the overall treatment plan.

D. If a patient does NOT meet the criteria for diagnosing CRPS as given in Table I, but the attending physician feels that the patient has sympathetically maintained pain, you may request authorization for a diagnostic sympathetic block. Requests to the state fund for a diagnostic sympathetic block should be sent to the L&I Office of the Medical Director for review.

7. AN OVERVIEW OF TREATMENT

Experts in CRPS believe the probability of a patient developing this condition can be reduced by early mobilization/activation following

injury or surgery. Conversely, unnecessarily prolonged immobilization following injury or surgery may set the stage of iatrogenic CRPS. Therapy for CRPS should be directed toward the goals of physical restoration and pain control. Details regarding treatment are presented in Tables 1 and 2 located at the end of this Guideline.

A. Physical Restoration

Experts agree that CRPS patients usually become trapped in a vicious cycle in which guarding and activity restrictions perpetuate the pain of CRPS. Therapy for CRPS should be directed toward breaking the pain cycle by having patients participate in a progressive activation program for the affected limb.

1. Because patients usually resist using the affected extremity, the physical restoration program generally requires supervision by a physical therapist or occupational therapist.
2. Involvement of a physical or occupational therapist is important so that repeated measurements of a patient's functional capacity can be made.
3. The frequency with which a patient receives physical or occupational therapy must be individualized by the attending physician.
4. Physical or occupational therapy occasionally continues beyond the time period during which pain control interventions such as sympathetic blocks are administered. Such prolonged therapy will be authorized as long as there is evidence of ongoing improvement of function of the limb.
5. Patients need to understand they must use their symptomatic limb in the course of their usual daily activities as well as during physical or occupational therapy sessions. Patients must commit themselves to physical restoration on a 24-hour per day basis.

B. Pain Control

1. Interventions to reduce pain are typically needed so that patients can get enough relief to participate in an activation program.
2. It is crucial that pain control interventions be linked closely with physical/occupational therapy. Physical or occupational therapy sessions should be scheduled as soon as possible after a sympathetic block. The interval between block and therapy should always be less than 24-hours. In general, physical/occupational therapy should be directed toward activation and desensitization in the affected limb. Details are given in Table 2.
3. Clinicians use a variety of medications to control pain in patients with CRPS. These include alpha adrenergic blockers, corticosteroids, antidepressants, anti-seizure medications, mexiletine and opiates. The Department of Labor and Industries has no formal guideline regarding a specific medication regimen for CRPS.

C. Sympathetic Blocks

1. In a patient who meets criteria for CRPS, up to 3 sympathetic blocks will be authorized to allow the attending physician to determine whether the patient has sympathetically mediated pain.
2. Additional blocks will be authorized ONLY if there is evidence from the first three that the patient has sympathetically mediated pain.

3. The physician who performs each sympathetic block should document:
   (a) Measurable evidence that a sympathetic blockade in the target limb was achieved – e.g., hand/foot temperature before and after the block, observed color changes and/or venodilation.
   (b) The extent and duration of the patient's pain relief, based on a pain diary.

4. A patient should be seen by a physical or occupational therapist during the time interval when a sympathetic block would be expected to have an effect – that is, within a few hours of the block. The therapist should document the functional status of the patient's symptomatic limb during the therapy session.
5. The attending physician or the physician performing sympathetic blocks should correlate the information previously described n #3 and #4 to determine whether a block has produced the intended effects on pain, function and observable manifestations of CRPS.

D. Psychological Treatment

The clinical course of many patients with chronic pain, such as those with CRPS, may be complicated by pre-existing or concurrent psychological or psychosocial issues. A one time psychological/psychiatric consultation may be requested to assist in the evaluation of such patients.

For those patients you feel require treatment for psychological/psychiatric disorders, authorization for such treatment will be considered only under the following conditions:

The psychological/psychiatric consultation has led to a psychiatric diagnosis (that is, a DSM4 diagnosis),
AND 1) **EITHER** the diagnosed psychiatric condition must be considered causally related to the industrial injury,
2) **OR** the diagnosed condition must be retarding recovery from the industrial injury.

E. Treatment Phases

Treatment is divided into six-week phases. A maximum of three phases may be authorized. The second phase will be authorized only if the first phase has led to demonstrable functional improvement. The third phase may be authorized only if the first and second phases have led to demonstrable functional improvement.

1. In the first six-week phase, up to 5 sympathetic blocks will be authorized (along with other accepted conservative measures such as medication management).
2. During the second six-week phase, a total of 3 sympathetic blocks will be authorized.
3. Up to 3 more sympathetic blocks may be authorized for patients who go on to the third phase of treatment.

F. Hospitalization

Hospitalization is rarely appropriate in the treatment of CRPS. The only exception to this is that a CRPS patient might have an orthopedic condition that is

amenable to surgery. Because CRPS patients are at high risk for flares after surgery, it is reasonable for such a patient to be admitted to a hospital prior to surgery so that aggressive pain control measures may be undertaken preoperatively.

G. Sympathectomy

Sympathectomies are not indicated for CRPS and are <u>NOT COVERED</u>.

8. REFERENCES

1. Janig W & Stanton-Hicks M (ed) Reflex Sympathetic Dystrophy: A Reappraisal. Seattle: IASP Press, 1996.
2. Merskey H & Bogdud N (ed) Classification of Chronic Pain (2nd ed). Seattle: IASP Press 1994.

Table 1
Labor And Industries
Criteria Number 13
Chronic Regional Pain Syndrome (CRPS)
Conservative Treatment Guideline

EXAMINATION FINDINGS & DIAGNOSTIC TEST RESULTS	**CONSERVATIVE CARE**
At least **four** of the following **must be present** in order for a diagnosis of CRPS to be made. ***EXAMINATION FINDINGS:*** 1. Temperature/color change 2. Edema 3. Trophic skin, hair, nail growth abnormalities 4. Impaired motor function 5. Hyperpathia/allodynia 6. Sudomotor changes ***DIAGNOSTIC TEST RESULTS*** 7. Three-phase bone scan that is abnormal in pattern characteristics for CRPS. This test is not needed if 4 or more of the above examination findings are present. **SURGICAL INTERVENTION (SYMPATHETECTOMY) FOR TREATMENT OF THIS CONDITION IS NOT COVERED**	Early aggressive care is encouraged. Emphasis should be on improved functioning of the symptomatic limb. **FIRST SIX WEEKS OF CARE:** - Sympathetic blocks, maximum of **five**. Each block should be followed immediately by physical/occupational therapy. - Physical/occupational therapy should be focused on increasing functional level (see Table 2). - Other treatment, e.g., medication at MD's discretion as long as it promotes improved function. ***AFTER THE 1ST SIX WEEKS OF CARE:*** - Strongly consider psychiatric or psychological consultation if disability has extended beyond 3 months. - Continued physical/ occupational therapy based on documented progress towards goals established during first 6 weeks (referenced above). - Sympathetic blocks only if response to previous blocks has been positive, maximum of 3** every six weeks for a maximum of 12 weeks. ****A maximum of 11 blocks can be delivered over the total 18 week period.**

Table 2

Labor And Industries
Criteria Number 13
Chronic Regional Pain Syndrome (CRPS)
Conservative Treatment Guideline

PROTOCOL FOR PHYSICAL THERAPY/OCCUPATIONAL THERAPY FOR CRPS

1. Evaluation should:
- **A.** Include a date of onset of original injury (helpful in determining if early or late stage) and a date of onset of the CRPS symptoms.
- **B.** Establish a baseline for strength and motion.
- **C.** Establish a baseline for weight bearing for lower extremity.
- **D.** If lower extremity, evaluate distance able to walk and need for assistive device.
- **E.** If upper extremity, establish a baseline for grip strength, pinch strength and shoulder range of motion.
- **F.** If possible, objectify swelling (e.g., do volume displacements).
- **G.** Define functional limitations.

2. Set specific functional goals for treatment related to affected extremity.

3. All treatment programs should include a core of:
- **A.** A progressive active exercise program, including a monitored home exercise program.
- **B.** Progressive weight bearing for the lower extremity (if involved).
- **C.** Progressive improvement of grip strength, pinch strength and shoulder range of motion of the upper extremity (if involved).
- **D.** A desensitization program.

4. For specific cases, additional treatment options may be indicated to enhance effectiveness of the above core elements. Documentation should reflect reasons for these additional treatment options.

5. Documentation should include:
- **A.** At least every two weeks, assessment of progress towards goals.
- **B.** Response to treatment used in addition to core elements (listed above in section 3).
- **C.** Evidence of motivation and participation in home exercise program, i.e., diary or quota system.